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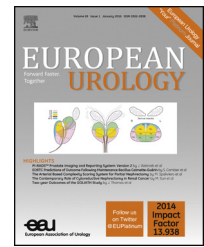
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Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Quantifying the Transition from Active Surveillance to Watchful Waiting Among Men with Very Low-risk Prostate Cancer

Mieke Van Hemelrijck^{a,b,†,*}, Hans Garmo^{a,c,†}, Lars Lindhagen^d, Ola Bratt^{e,f},
Pär Stattin^{g,h}, Jan Adolfssonⁱ

^a Cancer Epidemiology Group, Division of Cancer Studies, King's College London, London, UK; ^b Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; ^c Regional Cancer Centre Uppsala, Akademiska Sjukhuset, Uppsala, Sweden; ^d Uppsala Clinical Research Centre, Uppsala, Sweden; ^e Department of Translational Medicine Urology, Division of Urological Cancer, Lund University, Lund, Sweden; ^f CamPARI Clinic, Department of Urology, Cambridge University Hospitals, Cambridge, UK; ^g Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; ^h Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University Hospital, Umeå, Sweden; ⁱ CLINTEC Department, Karolinska Institute, Stockholm, Sweden

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Abstract

Background: Active surveillance (AS) is commonly used for men with low-risk prostate cancer (PCa). When life expectancy becomes too short for curative treatment to be beneficial, a change from AS to watchful waiting (WW) follows. Little is known about this change since it is rarely documented in medical records.

Objective: To model transition from AS to WW and how this is affected by age and comorbidity among men with very low-risk PCa.

Design, setting, and participants: National population-based healthcare registers were used for analysis.

Outcome measurements and statistical analysis: Using data on PCa characteristics, age, and comorbidity, a state transition model was created to estimate the probability of changes between predefined treatments to estimate transition from AS to WW.

Results and limitations: Our estimates indicate that 48% of men with very low-risk PCa starting AS eventually changed to WW over a life course. This proportion increased with age at time of AS initiation. Within 10 yr from start of AS, 10% of men aged 55 yr and 50% of men aged 70 yr with no comorbidity at initiation changed to WW. Our prevalence simulation suggests that the number of men on WW who were previously on AS will eventually stabilise after 30 yr. A limitation is the limited information from clinical follow-up visits (eg, repeat biopsies).

Conclusions: We estimated that changes from AS to WW become common among men with very low-risk PCa who are elderly. This potential change to WW should be discussed with men starting on AS. Moreover, our estimates may help in planning health care resources allocated to men on AS, as the transition to WW is associated with lower demands on outpatient resources.

Patient summary: Changes from active surveillance to watchful waiting will become more common among men with very low-risk prostate cancer. These observations suggest that patients need to be informed about this potential change before they start on active surveillance.

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[†] These authors contributed equally to this work.

* Corresponding author. Cancer Epidemiology Group, Division of Cancer Studies, King's College London, Bermondsey Wing, Guy's Hospital, London SE1 9RT, UK. Tel. +44 20 71887904.

E-mail address: mieke.vanhemelrijck@kcl.ac.uk (M. Van Hemelrijck).

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1. Introduction

Active surveillance (AS) is a common management strategy for men with low-risk prostate cancer (PCa). AS, with the intention to start curative treatment at the time of progression, may preserve some of the benefits of screening by minimising the harm caused by overtreatment of indolent cancer [1–6].

AS has been used for management of men with low-risk PCa for more than a decade [6]. AS ends when curative treatment is started, when changing to watchful waiting (WW), or when death occurs [2–6]. WW, also called symptom-guided treatment, is a management option for men with low-risk PCa who have a limited life expectancy and for whom curative treatment at the time of progression is not deemed to be beneficial. Men on WW typically start on androgen deprivation therapy (ADT) when symptomatic progression occurs [5,7].

The PCa among a large proportion of men on AS will not progress, and these men will thus remain on AS for a long period of time. Their life expectancy will at some point become so short that curative treatment is no longer indicated, leaving WW as the remaining option. This change to WW has an impact on health care resource allocation, as it is associated with less intense follow-up (eg, no more biopsies). However, the precise time point for this change is rarely defined and documented in medical records. Only a few studies to date have investigated the change from AS to WW, as most studies on AS focus on the change to curative treatment [8,2,9].

The aim of the current study was to assess the change from AS to WW among men with very low-risk PCa. We adopted a state transition model [10] using comprehensive data on cancer characteristics and comorbidity to estimate the proportion of men who change from AS to WW and when this occurs [11,12]. We also investigated how this change from AS to WW is affected by age and comorbidity.

2. Patients and methods

2.1. Study population and data collection

In 2012, the National Prostate Cancer Register (NPCR) of Sweden was record linked to a number of other population-based registers using the Swedish personal identity number [11,12]. The linkage was updated in 2014. The NPCR became nationwide in 1998 and captures more than 98% of all newly diagnosed PCa compared to the Swedish Cancer Registry. NPCR keeps detailed information on tumour characteristics and primary treatment at the time of diagnosis. Combining data from the National Patient Register and the National Prescribed Drug Register regarding subsequent treatment changes with the NPCR and other health care registers and demographic databases resulted in PCBaSe^{Traject}, which is the basis for this study [12]. To assess the burden of concomitant disease, all changes in Charlson comorbidity index (CCI) [16] during the course of follow-up were retrieved from the National Patient Register and the Swedish Cancer Register. The date of prostate biopsy as registered in the National Patient Register was used as an indication of ongoing AS. More specifically, WW and AS were both registered in the NPCR as deferred treatment up to 2007, after which they were distinguished. Their definitions are consistent with international guidelines [2–6]. AS is

defined as a strategy in which the man is followed closely and curative treatment is initiated if there is evidence of disease progression. By contrast, WW is usually performed for men with a limited life expectancy, and ADT is initiated if symptomatic progression occurs [14].

We selected men with very low-risk PCa who started AS. Very low-risk PCa was defined as Gleason score ≤ 6 with prostate-specific antigen (PSA) ≤ 10 ng/ml, prostate volume < 90 cm³, PSA density < 0.2 , 6–12 core biopsies performed, T1c or T2, positive cores $\leq 33\%$, and cancer length ≤ 6 mm as defined by Loeb et al [13] in a previous PCBaSe study. We added an additional age restriction (age 40–75 yr) in accordance with the Swedish recommendation for AS [14]. Biopsy-related information was not available for all men, and therefore we used multiple imputation based on chained equations [15] to create five imputation data sets in which it was possible to define whether the above criteria were fulfilled or not. Data were missing for cancer length in biopsies (51%), percentage positive cores (40%), and prostate volume (37%); complete data were available for 46% of men. The imputation was based on all data presented in Table 1 as well as time-to-event data. Furthermore, since the NPCR did not make a distinction between WW and AS before 2007, this group of men ($n = 856$) are classified as unknown deferred treatment (DT). To determine whether these men were on AS or WW, we treated this as a missing data problem (Supplementary material). Finally, men on WW as their primary treatment were included in the study to facilitate the estimation of changes from AS to WW.

To enhance the precision of our estimates, we used the above methods after inclusion of men with low-risk PCa (Gleason score ≤ 6 , stage \leq T1c/T2, PSA < 10 ng/ml) who did not fulfil the above-mentioned definition of very low-risk PCa. In Sweden, a large proportion of men with low-risk PCa are also on AS. For instance, 74% of men with low-risk, but not very low-risk, PCa were assigned to AS in 2014 [8]. More specifically, we used information for men with low-risk PCa to obtain additional information on treatment and comorbidity changes, which was then included in our models. Detailed results for men with low-risk PCa who did not fulfil the definition of very low-risk PCa are presented in the Supplementary material.

The Research Ethics Board at Umeå University approved this study.

2.2. Statistical methods

The change from AS to WW involves a competing risks problem. In addition to the two competing risks described above (ie, the change to curative treatment [radical prostatectomy or radiotherapy] or death), we also considered AS failure as a competing risk. AS failure was defined as initiation of ADT for men on AS without any signs of disease progression. Since the change from AS to WW was not documented in PCBaSe, we could not calculate cumulative incidence proportions as defined by Kalbfleisch and Prentice [16] nor could we use standard imputation techniques.

We therefore investigated changes from AS using a state transition model [10,17]. We estimated the probability of treatment changes (transition probabilities) between predefined treatments (states), as illustrated by the arrows (transitions) and circles (states) in Fig. 1. Each patient was followed from the initial state (yellow boxes) until ending up in an absorbing state (orange boxes). All state transition models were developed in accordance with the good practice guidelines of the ISPOR Modeling Task Force and the Society for Medical Decision Making [18].

Figure 1A shows the intended study. However, as no data are available to directly investigate the change from AS to WW, we also included men on WW as a primary treatment in our analyses (Figure 1B). Apart from transitions to curative treatment, WW, and AS failure, we also added the possibility of a transition from AS to ADT (AS \rightarrow WW \rightarrow ADT). As our main aim was to study the transition from AS to WW, secondary transitions (eg, radical prostatectomy \rightarrow death) are not shown in

Table 1 – Baseline characteristics at time of prostate cancer diagnosis by initial treatment category for men in the study population in PCBaSe (data taken from imputation data set 1)

	AS (n = 5963)	WW (n = 537)	DT (n = 856)	All (n = 7356)
Median age, yr (IQR)	65.3 (61.0–68.8)	72.1 (68.4–75.6)	69.1 (63.5–72.2)	66.0 (61.6–69.8)
Age, n (%)				
≤55 yr	364 (6.1)	6 (1.1)	41 (4.8)	411 (5.6)
56–60 yr	873 (14.6)	22 (4.1)	78 (9.1)	973 (13.2)
61–65 yr	1627 (27.3)	55 (10.2)	149 (17.4)	1831 (24.9)
66–70 yr	2095 (35.1)	112 (20.9)	208 (24.3)	2415 (32.8)
71–80 yr	1004 (16.8)	280 (52.1)	380 (44.4)	1664 (22.6)
≥81 yr		62 (11.5)		62 (0.8)
Year of diagnosis, n (%)				
1992–1997			27 (3.2)	27 (0.4)
1998–2004	157 (2.6)	40 (7.4)	388 (45.3)	585 (8.0)
2005–2008	1037 (17.4)	151 (28.1)	359 (41.9)	1547 (21.0)
2009–2011	1977 (33.2)	208 (38.7)	47 (5.5)	2232 (30.3)
2012–2014	2792 (46.8)	138 (25.7)	35 (4.1)	2965 (40.3)
CCI, n (%)				
0	4414 (74.0)	368 (68.5)	692 (80.8)	5474 (74.4)
1	754 (12.6)	94 (17.5)	86 (10.0)	934 (12.7)
2	421 (7.1)	40 (7.4)	56 (6.5)	517 (7.0)
3+	374 (6.3)	35 (6.5)	22 (2.6)	431 (5.9)
T stage, n (%)				
T1c	5213 (87.4)	412 (76.7)	662 (77.3)	6287 (85.5)
T2	750 (12.6)	125 (23.3)	194 (22.7)	1069 (14.5)
N stage, n (%)				
N0	674 (11.3)	38 (7.1)	19 (2.2)	731 (9.9)
Nx	5289 (88.7)	499 (92.9)	837 (97.8)	6625 (90.1)
Gleason score, n (%)				
2–6	5958 (99.9)	536 (99.8)	794 (92.8)	7288 (99.1)
Missing ^a	5 (0.1)	1 (0.2)	62 (7.2)	68 (0.9)
PSA, n (%)				
0–3.0 ng/ml	546 (9.2)	31 (5.8)	91 (10.6)	668 (9.1)
3.1–6.0 ng/ml	3813 (63.9)	281 (52.3)	441 (51.5)	4535 (61.7)
6.1–10.0 ng/ml	1604 (26.9)	225 (41.9)	324 (37.9)	2153 (29.3)
Median LCBC, mm (IQR)	1.5 (1.0–3.0)	2.0 (1.0–3.5)	1.5 (1.0–2.6)	1.6 (1.0–3.0)
Data missing, n (%)	1289 (21.6)	200 (37.2)	773 (90.3)	2262 (30.8)
Median PV, cm ³ (IQR)	42 (34–54)	48 (37–58)	45 (35–59)	43 (34–55)
Data missing, n (%)	647 (10.9)	121 (22.5)	767 (89.6)	1535 (20.9)
Median PPC (IQR)	0.10 (0.10–0.20)	0.17 (0.10–0.20)	0.10 (0.10–0.17)	0.10 (0.10–0.20)
Data missing, n (%)	493 (8.3)	106 (19.7)	760 (88.8)	1359 (18.5)
Mode of detection, n (%)				
Screening	3648 (61.2)	219 (40.8)	303 (35.4)	4170 (56.7)
LUTS	1555 (26.1)	213 (39.7)	226 (26.4)	1994 (27.1)
Other symptoms	648 (10.9)	96 (17.9)	232 (27.1)	976 (13.3)
Unknown	112 (1.9)	9 (1.7)	95 (11.1)	216 (2.9)

AS = active surveillance; WW = watchful waiting; DT = unknown deferred treatment; CCI = Charlson comorbidity index; LCBC = length of cancer in biopsy cores; PPC = proportion of cores with cancer; PV = prostate volume; LUTS = lower urinary tract symptoms.

^a In the case of missing Gleason score, all men had World Health Organisation grade 1.

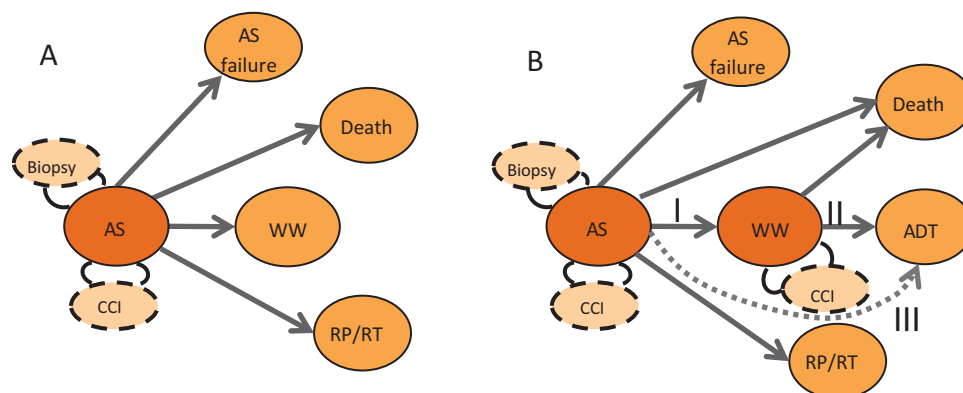


Fig. 1 – State transition model defining transitions (arrows) between states (circles): active surveillance (AS) to curative treatment (radical prostatectomy/radiotherapy, RP/RT), death, AS failure, or watchful waiting (WW) and androgen deprivation therapy (ADT). Red circles represent transient stages and orange circles represent absorbing states. The light orange circles represent additional information gathered to facilitate the estimation of transition probabilities (biopsy and Charlson comorbidity index [CCI]).

Figure 1A because these were not intended to be studied in the current study.

The basic assumption for all our modelling is that the age-specific transition rates from WW to ADT are similar for men starting on WW ($WW \rightarrow ADT$) as for those starting on AS and those changing to ADT via WW ($AS \rightarrow WW \rightarrow ADT$). In men starting on WW, the transition to ADT is observable in the data, and therefore the transition rate for $WW \rightarrow ADT$ can be estimated directly as shown in Figure 1B (arrow II). Moreover, since the start of ADT in the event chain $AS \rightarrow WW \rightarrow ADT$ (arrow III) can be observed, it is also possible to indirectly estimate the transition rate for $AS \rightarrow WW$ (arrow I) using the above basic assumption (Supplementary material).

2.2.1. State transition model

Our state transition model used discrete time steps of 4 wk. During each time step, a man either remained in his state or moved to a new state. Each man was followed from the date of diagnosis or January 1, 2006, whichever came last (left truncation), until reaching an absorbing state or the end of follow-up (December 31, 2014), whichever came first. Using the date January 1, 2006 as study entry allowed for a 6-mo run-in period, as ADT treatments were identified from the Swedish Prescribed Drug Register, which only started on July 1, 2005.

Since the person-time on AS is unknown, the probability of directly observable transitions such as death and curative treatment cannot be estimated via logistic regression. We therefore created a single large model incorporating all transitions in Figure 1B and their relation to

covariates such as age, time spent in a specific state, time since diagnosis, and CCI. The regression coefficients were fitted using maximum likelihood methods. The Supplementary material provides further details on the model specifications.

In this model we also included additional indirect information as follows. A biopsy was considered as an indication for remaining on AS, whereas a long period without biopsies increased the likelihood of a transition to WW. Initiation of curative treatment indicated that a man had been on AS until that point in time. Initiation of ADT was considered as evidence of a previous transition to WW in the model. However, there were exceptions: When a young man with low comorbidity (CCI 0) received ADT shortly after PCa diagnosis, this was defined as an AS failure (Supplementary Table 2). A separate state-transition probability was created for this situation (Supplementary material) [2–6].

2.2.2. Estimations

To visualise the fitted model in terms of the timing and occurrence of state transitions in accordance with Figure 1B, we calculated estimations for men with specific age and CCI scores [10]. First, we assessed the sensitivity of our assumption of similar transition rates for $AS \rightarrow WW$ and $AS \rightarrow WW \rightarrow ADT$. We therefore estimated the cumulative incidence of $AS \rightarrow WW$ transitions based on five variations of our assumption using relative transition rates of 50%, 80%, 100%, 150%, and 200%, but noticed very little difference. For instance, for men aged 55 yr, the proportion of men who switched to WW within 10 yr was 15%, 13%, 13%, 11%, and 10%, respectively, for the five transition rates. Similarly, for men aged 70 yr,

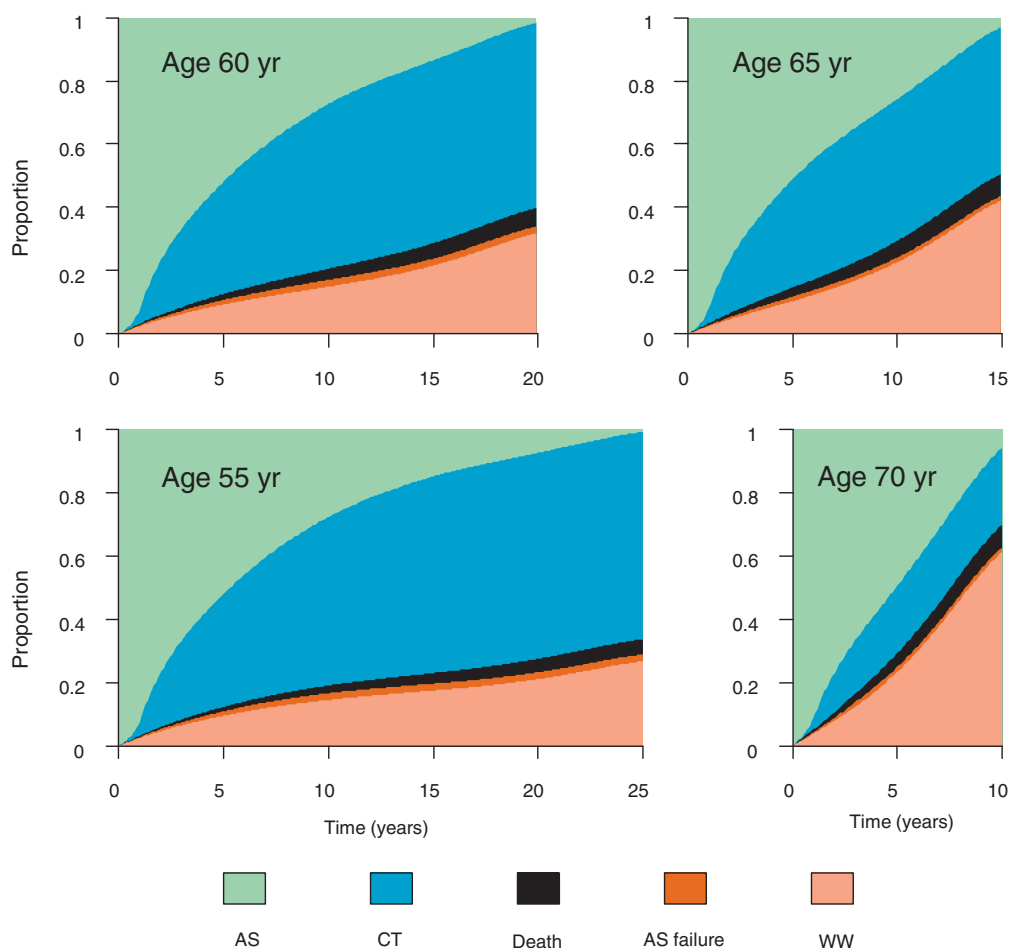


Fig. 2 – Proportion of men on active surveillance (AS) who remained on AS, failed AS, changed to watchful waiting (WW) or curative therapy (CT), or died as the first event. All men presented with Charlson comorbidity index of 0 at the time of prostate cancer diagnosis.

the corresponding proportions were 52%, 50%, 51%, 47%, and 46%. All the results presented are therefore based on equal rates (100%).

In the main analysis, we estimated transitions for two different scenarios in which all men eventually transitioned from AS to another state (Fig. 1B). In the first scenario we focused on men aged 55, 60, 65, or 70 yr with CCI = 0 starting on AS. More details on the methods used for these estimations can be found in the Supplementary material. For the second scenario, we performed estimations for a theoretical cohort created using an annual inflow of men on AS selected as annual bootstrapped samples of 1000 men from the pool of men on AS in NPCR diagnosed with very low-risk PCa between 2010 and 2014. The annual inflow of men was continued for a period of 40 yr. In both scenarios, CCI was updated according to an independent model, as described below.

2.2.3. CCI model

A model for CCI development over time was required for the estimations described above. In brief, this was achieved by estimating whether a change in CCI took place or not for each time step. If a change in CCI had occurred, the size of this change was estimated from a Poisson model, together with a separate model handling CCI changes ≥ 6 . Details of this method can be found elsewhere [19].

3. Results

A total of 17 783 men with low-risk PCa on AS, WW, or DT were recorded in NPCR between 1992 and 2014 (Supplementary Table 1). After imputation of missing data, we identified 7278 men with very low-risk PCa (median over five imputation data sets with size ranging from 7169 to 7388).

Table 1 shows the cohort characteristics at the time of PCa diagnosis for imputation data set 1 by initial treatment (AS, WW, DT). The number of men with very low-risk PCa on AS increased during later time periods. Men on AS were younger (mean age 65 yr) than men on WW (mean age 72 yr). The mean age in the DT group was 67 yr.

Figure 2 shows the estimated proportion of men (CCI = 0 at time of PCa diagnosis) who remained on AS, failed AS, changed to radical treatment, changed to WW, or died as a first event following AS over time. Older age at start of AS was associated with a greater proportion of men transitioning WW, whereas younger age was associated with a greater proportion of men undergoing radical treatment. For instance, within 10 yr from AS initiation, 10% of men aged 55 yr with CCI = 0 at start of follow-up were estimated to transition to WW, compared to 50% of men aged 70 yr.

Figure 3 shows the estimated prevalence of men who either remained on AS or transitioned to WW over a period of 40 yr according to our estimation model based on an annual inflow of 1000 men with very low-risk PCa on AS. The prevalence of men on WW increased slowly during the first years, with the highest rate of prevalence change occurring during 10–20 yr, and stabilised after 30 yr. The age-specific prevalence simulations indicate that prevalence change occurred less frequently for younger men.

Tables 2 and 3 further quantify these prevalence changes and show that the time on AS decreases with age, whereas the proportion of men changing to WW increases with age. Overall, men with very low-risk PCa remained on AS for

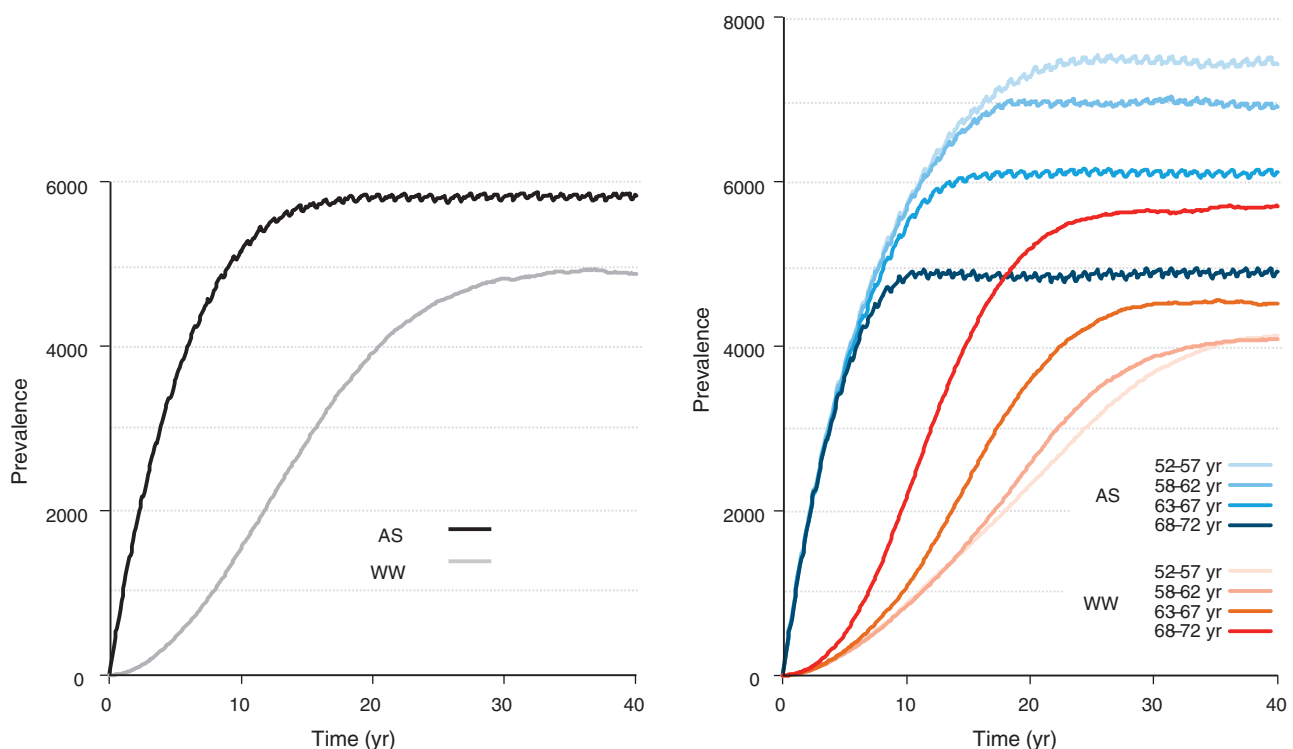


Fig. 3 – Estimated number of men who remained on active surveillance (AS) or changed to watchful waiting (WW) over a period of 40 yr for all ages combined and for age groups 52–57 yr, 58–62 yr, 63–67 yr, and 68–72 yr. Estimation included an annual inflow of 1000 newly diagnosed men with very low-risk prostate cancer in each stratum.

Table 2 – Median time on AS and proportion transitioning to WW and absorbing states as estimated from the prevalence models based on annual inflow of 1000 patients/yr in each stratum

	Age at prostate cancer diagnosis				All
	53–57 yr	58–62 yr	63–67 yr	68–72 yr	
Median time on AS, yr (IQR)	5.4 (2.2–10.7)	5.3 (2.2–10.4)	5.1 (2.1–9.7)	4.6 (2.1–7.7)	4.7 (2.0–8.7)
Patients reaching WW as first event (%)	29.2	34.4	45.2	62.3	48.3
Patients reaching CT as first event	61.0	54.3	42.2	24.4	39.6
Patients AS failure as first event (%)	2.2	2.1	2.0	2.2	2.3
Patients reaching death as first event (%)	7.6	9.2	10.6	11.1	9.8

AS = active surveillance; CT = curative treatment; IQR = interquartile range; WW = watchful waiting.

Table 3 – Median time on WW and proportion of patients reaching absorbing states as estimated from the prevalence models based on annual inflow of 1000 patients/yr in each stratum

	Age at prostate cancer diagnosis				All
	53–57 yr	58–62 yr	63–67 yr	68–72 yr	
Median time on WW, yr (IQR)	12.6 (5.9–21.5)	10.3 (5.0–17.2)	8.8 (4.2–14.5)	8.0 (3.8–13.0)	8.7 (4.2–14.4)
Patients reaching ADT as second event (%)	28.7	27.9	27.1%	26.5	26.9
Patients reaching death as first event (%)	71.3	72.1	72.9%	73.5	73.1

ADT = androgen deprivation therapy; IQR = interquartile range; WW = watchful waiting.

approximately 5 yr (median), and 48% changed to WW over a life course (approximated by 40 yr in our simulations; Table 2). Once a transition to WW had occurred, these men remained in this state for a median time of 9 yr (Table 3).

4. Discussion

We evaluated the change from AS to WW for men with very low-risk PCa using a large, population-based representative sample of men with very low-risk PCa in Sweden. Our estimations indicate that almost half of men with very low-risk PCa starting AS will eventually change to WW. This proportion increased with age and with comorbidity at time of AS initiation. Overall, the estimated median time on AS was 5 yr. Our prevalence simulation suggests that the number of men on WW who were previously on AS will eventually stabilise after 30 yr.

A few studies have investigated the change from AS to WW [8,2,9]. For instance, van As and colleagues [9] followed 326 men on AS for a median time of 22 mo and observed that 20% had deferred radical treatment, 5% changed to WW, 2% died of other causes, and 73% remained on AS. Klotz and colleagues [20] followed 993 men over a median time of 6 yr, and observed that 267 men went on to curative intervention and 15 died; no information on the change to WW was available. There are currently limited guidelines [21,22] on the change from AS to WW. The treatment pathways for men with very low-risk PCa also vary by country and are managed differently in various health care systems. In light of the increasing use of AS as primary management for men with low-risk PCa in Europe and the USA [1] (Loeb et al, unpublished data), there is a need for

guidelines to include criteria for the change from AS to WW. In daily clinical practise, follow-up during AS is probably not as intense as recommended by the guidelines, and the change from AS to WW may also not be clearly defined, either for the patient or for the urologist, as indicated by two recent publications based on Surveillance, Epidemiology, and End Results data [23,24].

Our simulation, which aimed to assess the overall change from AS to WW, suggests that in the near future there will be a rapid increase in the number of men who will transition from AS to WW. Our models indicate that this change from AS to WW will eventually become quite common. However, it is important to note that in clinical practice the actual transition to WW for an individual patient is not a probabilistic entity, but is rather based on age, CCI, the patient's preference, and clinical practice. Thus, our model is not intended as a tool for decision-making at an individual level. Although the vast majority of men who change from AS to WW will do so because of old age, some men change to ADT without a previous curative intervention: they either missed the opportunity for curative treatment or made an active choice to not undergo curative treatment. Our model estimates support the observation that a large proportion of men will reach the point at which a change to curative treatment is no longer an option. As this affects the intensity of follow-up (eg, fewer repeat biopsies), urologists should inform patients of this change [25], preferably before they start on AS.

The change from AS to WW not only affects patients and clinicians but also has an economic impact. Currently, protocols for AS [14,26,27] include frequent PSA testing, regular repeat biopsies, and in the future probably also repeat imaging [28]. The risk of infection after prostate

biopsy is not negligible [29]. Apart from the costs related to adverse events, there is also a potential cost linked to imaging [30,31]. A change from AS to WW may thus reduce health care expenditure as there will be fewer follow-up costs (eg, biopsies and related complications, imaging). Data on the change from AS to WW will not only help in estimating these costs, but also affect the validity of current health evaluations of AS effectiveness, as patients need information on the change from AS to WW to provide accurate patient-reported outcome measures and experience measures for AS [21].

A major strength of our study is the use of comprehensive data from PCBaSe^{Traject}, a large, nationwide, population-based database on PCa [13]. These data were used to assess transition rates in the models for the changes between different treatment options. Owing to the detailed information available, we could adjust our estimations for comorbidities and age, resulting in high internal validity. The models are therefore reliable. Even though our results were based on Swedish data only, we believe that the external validity of our study is acceptable for other populations with similar age-related rates of change in CCI. A limitation of our study is the scarce data on follow-up (eg, on repeat biopsies) as these are underreported in the Patient Register, and lack of information on the actual change from AS to WW for individual patients. Another limitation is that follow-up was not long enough to investigate causes of death for men with low-risk PCa on AS. With longer follow-up, a future study including this information could provide insight into whether AS was an appropriate choice and whether the change to WW was performed at the right time. Finally, it may be a limitation that we assumed similar transition rates for WW to ADT and AS to ADT for men of all ages, an assumption that cannot be verified by our data. However, we evaluated the effects of this assumption using different rates and noted very little differences in the results.

5. Conclusions

We estimated that changes from AS to WW become more common in men with very low-risk PCa, especially those who were elderly at the time of AS initiation. Our state transition models estimated that a large proportion of men with very low-risk PCa starting AS will change to WW. These observations suggest that patients need to be informed about this potential change before starting AS. Moreover, the impact of the change to WW on allocation of health care resources has probably been underestimated to date (less follow-up expenditure on WW compared to AS) and future guidelines on follow-up during AS should take this into account.

Author contributions: Mieke Van Hemelrijck had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Adolfsson, Van Hemelrijck, Lindhagen, Garmo.
Acquisition of data: Stattin, Garmo.

Analysis and interpretation of data: Van Hemelrijck, Garmo, Lindhagen.
Drafting of the manuscript: Van Hemelrijck.
Critical revision of the manuscript for important intellectual content: Lindhagen, Garmo, Adolfsson, Stattin, Bratt.
Statistical analysis: Garmo, Lindhagen.
Obtaining funding: Stattin, Adolfsson.
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Supervision: Van Hemelrijck, Adolfsson.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2016.10.031>.

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